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RADIATION CARCINOGENESIS*

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ONE hundred twenty-five years ago it required a singularly far-sighted group of medical men to found a society focused on the then new field of pathology. Theodor Schwann had discovered the cell as the basic unit of the animal body five years earlier. The year before the founding of the New York Pathological Society, Virchow graduated from the University of Berlin, and three years after the society was founded the first issue of *Virchow's Archiv* appeared in 1847. The society antedated by two years the discovery of ether as an anesthetic; by more than a quarter of a century both the discovery of bacteria and the dawn of modern surgery; and by more than half a century the discovery of ionizing radiation. In the healthy growth of this society such men as Francis Delafield, James Ewing, Milton Helpern, Eugene L. Opie, Theophil W. Prudden, Fred W. Stewart, Arthur P. Stout, Doug-

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las Symmers, and Francis Carter Wood have played a significant part. I hope that the group will continue its good work for many centuries more.

Long before that, however, I hope the various causes of cancer will have been clearly understood and preventive measures against the disease brought into effective use. Indeed it may be soon that a viral causation will have been established for some cases of leukemia in man as has been so well demonstrated for leukemia in mice[1] by Dr. Ludwik Gross. In the ultimate solution of the problems of cancer etiology the evidence contributed by radiation carcinogenesis will play a helpful role.

Five years after the discovery of x rays the first skin cancer resulting from exposure to them was reported.[2] Knowledge of the induction of other kinds of cancer by radiation followed slowly. Two intriguing facts about radiation and cancer have helped to spark scientific interest in their relations. Radiation cures cancer and also causes it and, further, does not cause it out of hand but usually after a latent period of years. This latent period might imply that cancer is not produced by a single cellular change but by a series of them.

The exact mode of action of radiation on the cell is not understood but, whatever it is, it must involve damage caused by transfer of energy to controlling mechanisms, either of the cell's metabolic and proliferative activities or of its enzyme systems. The amount of physical energy delivered to the cell by the radiation absorbed is usually far too little to account directly for the effect produced and hence must have been multiplied by some such means as these.

Several hypotheses have been developed to explain the mechanism of radiation carcinogenesis. The production of a somatic mutation leading to uncontrolled cell growth, acceleration of aging with its attendant high incidence of cancer, the activation of oncogenic viruses, altered environment of cells, and abnormal proliferation of cells following repeated attempts at repair of injury have all been proposed. I believe that more than one of these may well be involved, and probably additional hypotheses as yet undeveloped will be required to explain all the accumulated facts.

Thus far morphologic clues, the province of the pathologist, have provided not only the sure criteria for the diagnosis of cancer but also important leads as to the behavior of its many different forms.

The facts relating to the epidemiology of radiation-induced cancer

now have impressive impact. I shall present some of them, drawing largely on the data of the many workers in this field, with a few additions from my own experience. The earlier radiologists and radium workers showed excessive incidence of cutaneous cancer and of leukemia. The names of hundreds of scientific martyrs from among these pioneers are inscribed on the base of the monument at St. George's Hospital in Hamburg, Germany. Radium-dial painting provided many victims, among whom were those with osteogenic sarcoma and antral cancer, studied by Martland,[3] Evans,[4] and others. The mysterious pulmonary disease of the miners of Joachimsthal (now Jáchymov), Czechoslovakia, known and feared there since the Middle Ages, had been identified as lung cancer[5] and its causation related to radon and its daughter products present in the air of the mines. More recent examples of radiation carcinogenesis are the increased incidence of pulmonary cancer among some of our own uranium miners,[6] of cancer of the thyroid as demonstrated by Hempelmann and others[7] among those irradiated prophylactically for assumed thymic hyperplasia, and of leukemia among the Hiroshima-Nagasaki survivors studied by the Atomic Bomb Casualty Commission.[8] I propose to examine the incidence and nature of cancer in several of these groups in some detail in the hope of throwing some light on dose-effect relations and of stimulating interest in additional basic and clinical studies in this field.

Radiation dermatitis, sometimes followed years later by skin cancer, was seen all too often among early radiologists, usually on the left hand, which they placed in the x-ray beam for want of an easier way to check the efficiency of their crude devices. Sometimes doses of thousands of rads were accumulated. Atrophy, ulceration, focal hyperplasia, and eventually cancer developed in the epilated, dry, telangiectatic skin.[9] As might be expected from the relative number of epithelial cells contrasted with fibrocytes and also the relative frequency of mitosis between the two, carcinoma is many times more frequent as a manifestation of malignant change than is sarcoma. Sir Stanford Cade,[10] who has had long clinical experience, estimated that only a few of those with heavily irradiated skin developed cancer as a result. Fortunately, these lesions are rarely encountered today. Recently Albert[11] has studied cases here in New York where skin cancer had been induced by x irradiation in the scalps of some of those who had been temporarily epilated as children for the treatment of tinea capitis. Radiation-induced cancer

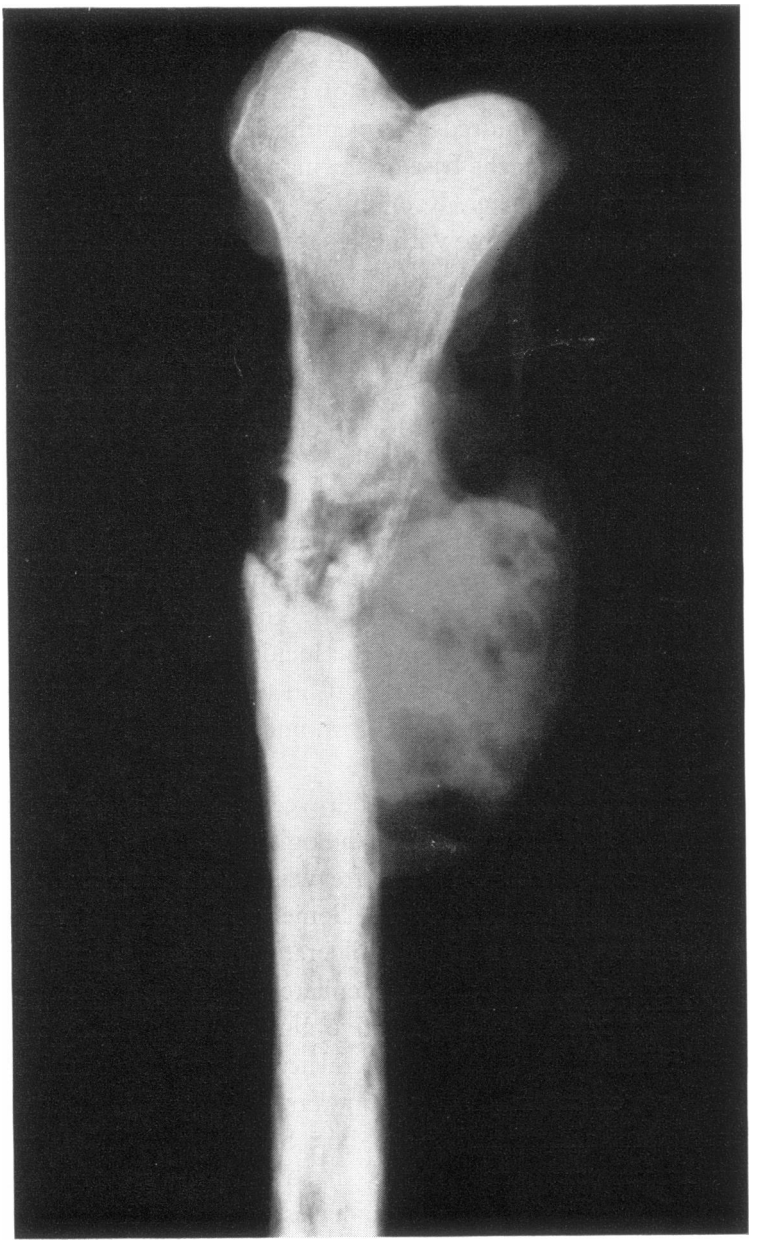

Fig. 1. Roentgenogram of dissected specimen. Radiation osteitis, osteogenic sarcoma, and pathologic fracture occurring in femur of a woman who had ingested radium-containing paint over 40 years previously.

of the skin cannot be differentiated from skin cancers caused by other noxious agents, nor for that matter can any form of cancer on the basis of histopathologic appearance or clinical behavior. Indeed, so far as any radiation-induced tumor is concerned, historical, epidemiologic, and other supporting evidence must be brought to bear. One possible exception is the characteristic and rare anaplastic hemangioendothelial sarcoma that sometimes develops as a sequel to thorium injection.[12] When tissue from the primary site is available, ionizing radiation can be deduced as a factor in causation by the changes suggestive or characteristic of radiation effect present in adjacent non-neoplastic tissue such as hyalinization of collagen, abnormal fibrocytes, and damaged blood vessels.

The dial painters, who pointed the brushes with their lips and so ingested and absorbed radioactive paint in minute amounts, accumulated this radium and in some instances thorium in their bones through selective absorption from the blood stream. The actual exposures to the paint were often brief, the occupation lasting only a year or so, but the difficulty of excretion of the radioactive metals and their deposition in bone produced life-long body burdens. From these deposits the alpha radiation bombarded for years osteocytes, osteoblasts, and osteoclasts. If the damage is less to osteoblasts and osteocytes than to osteoclasts the radiation osteitis that results is manifested chiefly by an increased density of bone to varying degrees, even eburnation. If damage to osteoblasts predominates, continuation of osteoclasis with insufficient bone formation results in rarefied foci. Both types often coexist in adjacent portions of bone, both are associated with pain, both may be present for long periods antecedent to the development of osteogenic sarcoma (Figure 1). As a result of the production of radon from the radium deposited in bones of the skull, high levels of radioactive gas may accumulate in the cavities of the bony sinuses (total local doses to the walls have reached 82,000 or more rads).[4] The resultant radiation damage to the mucous membranes of the walls caused epidermoid carcinoma to develop in some. The careful studies of Evans[4] and others have made dose-effect estimates possible. Evans has introduced the concept of a "practical threshold" below which cancers do not appear. This concept is somewhat unpopular in a period in which the hypothesis of a linear relation between dose and neoplastic effect has gained much support, especially as the application of linearity provides an

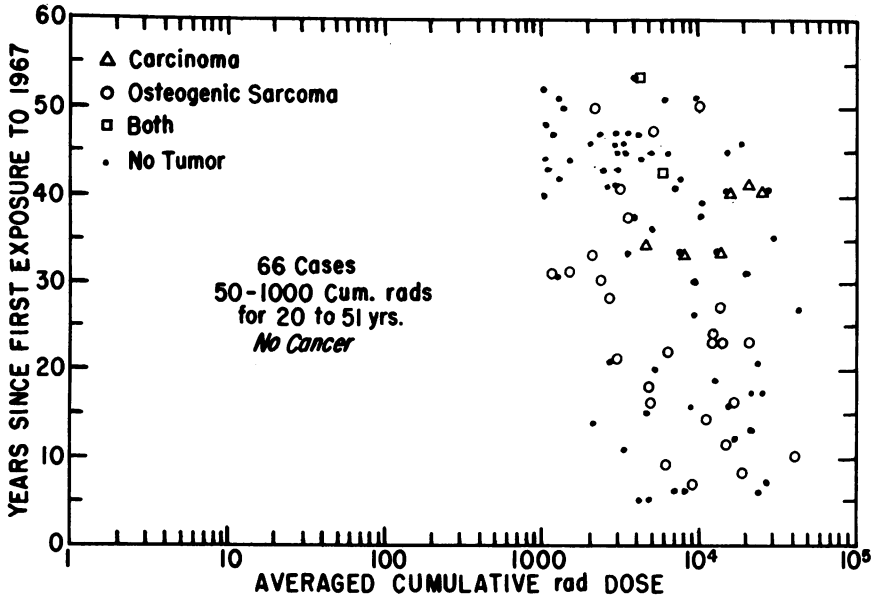

Fig. 2. Diagram showing the occurrence of osteogenic sarcoma and antral cancer in exposed radium watch-dial cases. Modified from Evans' diagram.[4]

added margin of safety in establishing permissible dose levels. Evans' data, based on 496 cases, are presented here in modified form (Figure 2). Until the dose level exceeds 1,000 rads there are no cancers. This, then, might be considered a "practical threshold," as Evans has suggested. At higher dose levels from one third to two thirds of the patients developed cancer, with a probable but ill-defined upward trend with increasing dose. However there is a drop in incidence at the highest dose levels, about 12,000 rads or more, perhaps due to the small size of the sample. This phenomenon of less carcinogenic effect at high dose levels has also been seen in some experiments in animals.

Osteogenic sarcoma, fortunately always a rare neoplasm, is a form of cancer that appears to be decreasing rather than increasing in incidence in the general population as is shown in the accompanying graph (Figure 3) of deaths from the disease in the United States. The rapid and unexplained decrease in mortality, curiously enough, coincides with the time when the level of radioactive fallout, supposed by some to be one of the causes of osteogenic sarcoma, was increasing. The fall-

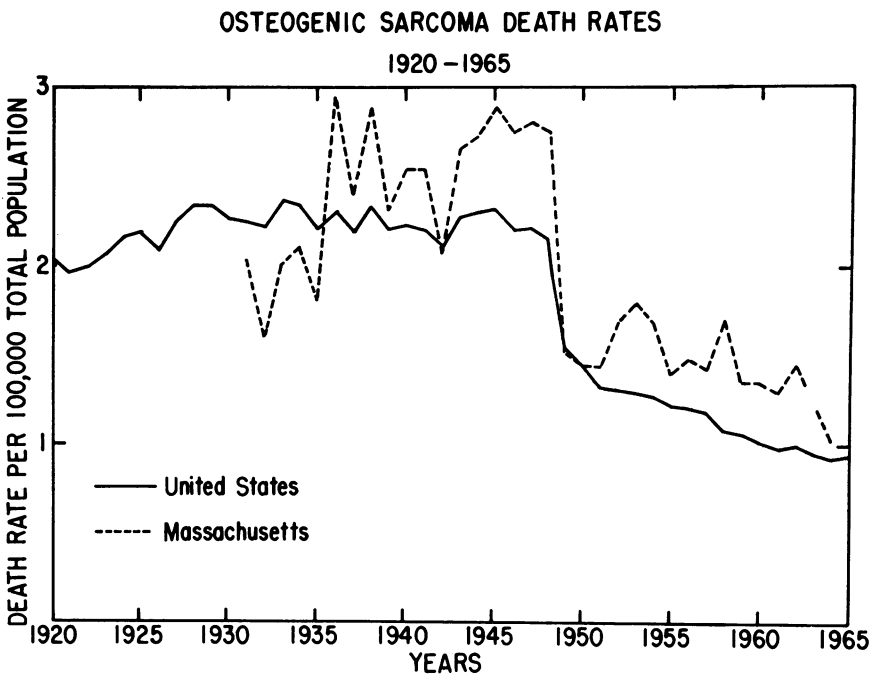

Fig. 3. Osteogenic sarcoma death rates.

out obviously did not reach a level that increased the prevalence of the disease.

The occurrence of another well-known cancer, that of the lung in uranium miners, is less well related to etiology. It is believed that inhaled alpha-emitting daughter products of radon present in the air of the mines and plated out in particulate form are inhaled and retained for long periods in the respiratory tree.[13] The alpha particles from these deposits are poorly penetrating; they reach only the more superficial cells but they have high linear energy transfer and so cause injury or death in those reached. Thus prolonged injury to bronchial epithelium results, which culminates in cancer in some instances. As already mentioned, exposure to the radon-rich air of the mines at Schneeberg, Germany, and Joachimsthal had long been known to increase the prevalence of lung cancer, and the same appears true of our western uranium mines. The risk there is now being lessened by ventilation and other protective measures. Exact dosimetry has been very difficult to establish, and cur-

rent estimates are subject to revision as additional data become available. These estimates have been made in the form of "working level months" (a combination of radiation level and time of exposure), each of which may indicate a dose to lung tissue of about 7 ± 5 rads.[6] Among 3,414 white underground miners working from 1950 to 1967, 62 lung cancers occurred, six times the expected number. This is much in excess of the rates reported for other United States miners, either hard rock or coal. Miners as a whole tend to show more pulmonary fibrosis and other lung diseases than the population as a whole. Meyer and Liebow[14] have noted that there may be a potentiating effect toward cancer in the combination of widespread pulmonary scarring of the so-called honeycombing type and exposure to cigarette smoke. Sixty of the 62 lung cancers appeared in men who were also cigarette smokers. However only one probable lung cancer has been found among 761 Navajo miners, largely nonsmokers. Other factors, such as chronic infection and inhalation of dust may play a potentiating or cocarcinogenic role. For example, in mice spontaneous cancer of the bronchus is rare. It may be induced, however, by a combination of influenza virus and artificial smog, though neither agent alone will produce the cancer. Bronchogenic cancer is also produced in rodents and other animals by large doses of radiation.

Epidemiologic studies of the uranium miners of the Colorado plateau have shown a rough dose-effect relation between radiation levels in the air of the mines and lung cancers. At higher dose levels (over 840 working level months of about 4,000 to 8,000 cumulative R) there has been consistent increased risk of lung cancer, which rose with exposure. At lower exposure levels there is still increased risk, but it is less and not clearly related to amount of exposure to radiation.

There has been much interest in the fact that many of the bronchial cancers have been of the undifferentiated or oat-cell type, as pointed out by Saccomanno.[15] However, general experience has been that cancers caused by radiation are not distinctive in type. The one example of a Joachimsthal uranium miner's lung cancer that I have, thanks to the late Dr. H. Sikl, happens to be a well-differentiated and heavily keratinized tumor, although a number of them have been undifferentiated. Many lung cancers seen in persons with no radiation exposure vary widely in histologic structure in different parts of the same tumor, so differentiation of cells can be relied upon for classification only if ade-

quate sampling of the total tumor mass has been done.

The evidence is strong that the excess lung cancer among white uranium miners is caused by radiation exposure and that the prevalence of the disease is increased by cigarette smoking, and possibly by other modes of pulmonary injury.

Another example of increased cancer prevalence due to radiation which also illustrates the long latent period involved is afforded by some cancers of the thyroid. These developed in some of those who had been irradiated as infants (90% were less than six months old) to reduce assumed thymic enlargement. Hempelmann and his associates[17] found not only an excess of thyroid cancer, some developing more than 20 years later, but an apparent excess of some other tumors as well, as compared with untreated siblings. Among the other tumors were leukemia and a benign bone lesion, osteochondroma. The range of exposures to x radiation in infancy that produced cancer later ranged from below 120 R to over 600 R. The excess incidence was clear-cut, nearly 100 times the expected incidence. However the incidence of thyroid cancer has not been shown to be clearly related to dose, perhaps because an insufficient number of cases have been available for study. Most of the thyroid cancers were of papillary type. In addition to these cases and series reported by other investigators, there are data from the Atomic Bomb Casualty Commission which indicate that the incidence of thyroid cancer among the Hiroshima-Nagasaki survivors has risen above that in other Japanese.[16] The natives who were exposed in 1954 at Rongelap and Uterik in the Marshall Islands to radiation from fresh fallout rich in radioactive iodine are being studied by Conrad[17] and his colleagues. A number of the exposed children have developed thyroid nodules. They may well provide further information on dose-effect relations.

There is evidence from sheep experimentally exposed to radioactive iodine produced from chemical processing of used reactor fuel in Hanford, Wash., that nodularity of the thyroid gland may be produced and that this nodularity may progress in some instances to the development of cancer.[18] As one would expect, because this nodularity is caused by damage to the thyroid and its attempted repair, there is a much better correlation between dose and the presence of nodules in the thyroid than there is between dose and the development of cancer. Likewise in man the frequency of appearance of nodules in the thyroid is greater

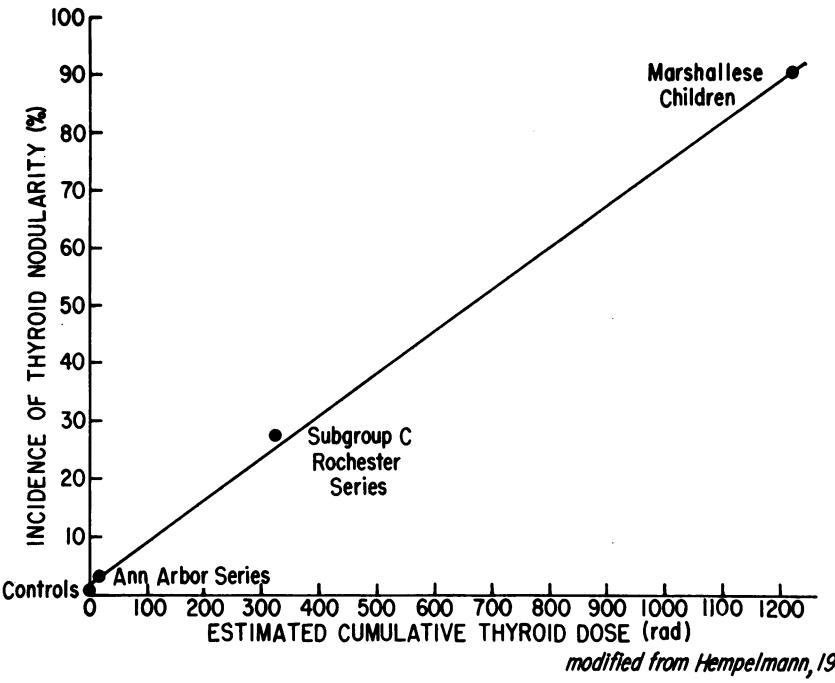

Fig. 4. Incidence of nodules in the thyroid as presented by Hempelmann[19] from his own data and that of others. Note the relative linearity of this type of thyroid damage.

than that of cancer and appears to precede the development of cancer. In the graph (Figure 4) the incidence of thyroid nodules is plotted as they have been encountered in several groups reported by Hempelmann[19] and others. With a low cumulative exposure of the thyroid there is a slight and probably questionable increase as evidenced by the Ann Arbor series.[20] In patients from the Rochester group who received more than 300 R the incidence is about 20%, and in the Rongelap children the incidence at 1,200 rad exposure is better than 90%. Here then, there appears to be a rough linear relation between cause and effect. If one adjusts the dose to allow for the protracted rate at which the radiation was received one finds an even steeper rise of thyroid nodularity with dose.

At present one can say that the incidence of thyroid cancer is increased by radiation, and that those exposed in infancy and childhood appear more susceptible than those exposed in adult life.

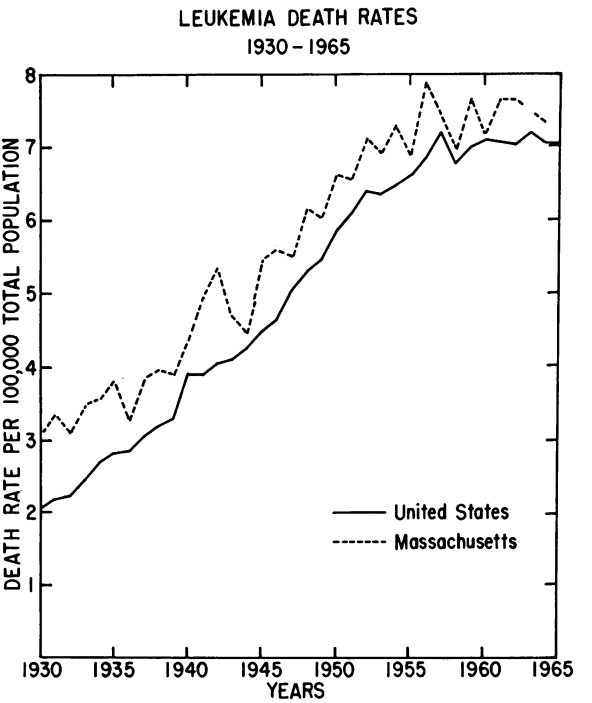

Fig. 5. Death rates from leukemia in the United States and in the Commonwealth of Massachusetts from 1930 to 1965. Note the sharp increase in incidence since 1960 and the tendency for the rate to level off in the late 1950s.

Blood dyscrasias have long been associated with exposure to radiation. Mme. Curie herself died of an unusual type of aplastic anemia. The fluctuations of blood cells following radiation exposure, small or large, have long been studied. In fact, the fluctuations in white blood cell count in survivors as well as mortality figures at Hiroshima and Nagasaki provided more accurate dosimetric information than did the initial calculations of the physicists. The most carefully studied of blood dyscrasias, both experimentally and clinically, is leukemia. A special challenge exists in that the leukemia death rate in the United States rose sharply from 1930 (well before the atomic age) and continued to do so until about 1955 where it seems to have leveled off (Figure 5). Induction of leukemia by radiation is perhaps better documented and correlated with dose than any other form of malignancy. A generation ago radiologists in the United States were found by March,[21] Ulrich,[22]

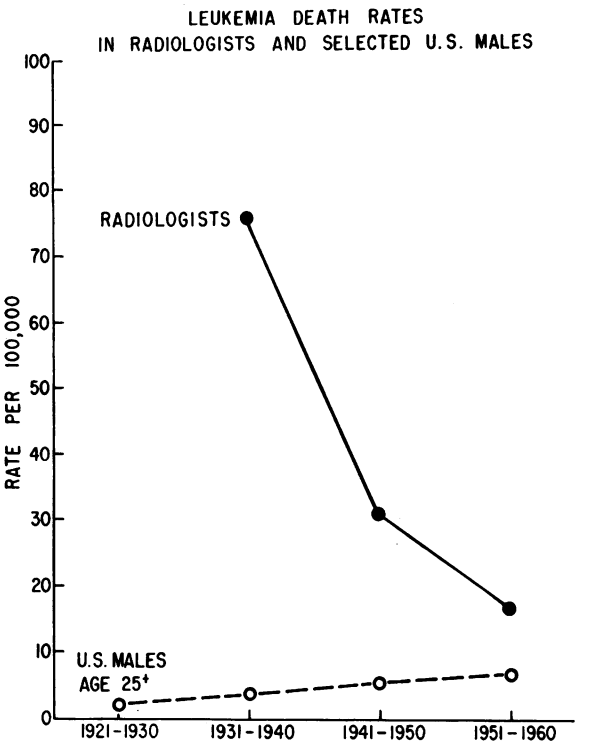

Fig. 6. The incidence of leukemia in radiologists compared with that of the population of the United States. Note the marked decrease in incidence among radiologists as greater precautions against overexposure have been taken.

and others[23, 24] to have a tenfold greater incidence of leukemia than control groups. As they learned to protect themselves better and reduced sharply the occupational exposures received, March's investigation[25] and my recent studies[26] (Figure 6) show the incidence has also been sharply reduced and indeed approaches the level in the general population. Among more than 3,000 Massachusetts dentists whom Miss O. M. Lombard and I[27] have followed for a decade, many of whom had long used x-ray apparatus but with caution, only one case of leukemia has been found.

The population most intensively studied in this regard is the group of Hiroshima-Nagasaki survivors. DeCoursey, Leroy, Liebow, Oughterson, and I,[28, 29] with our Japanese colleagues at the two cities, studied the

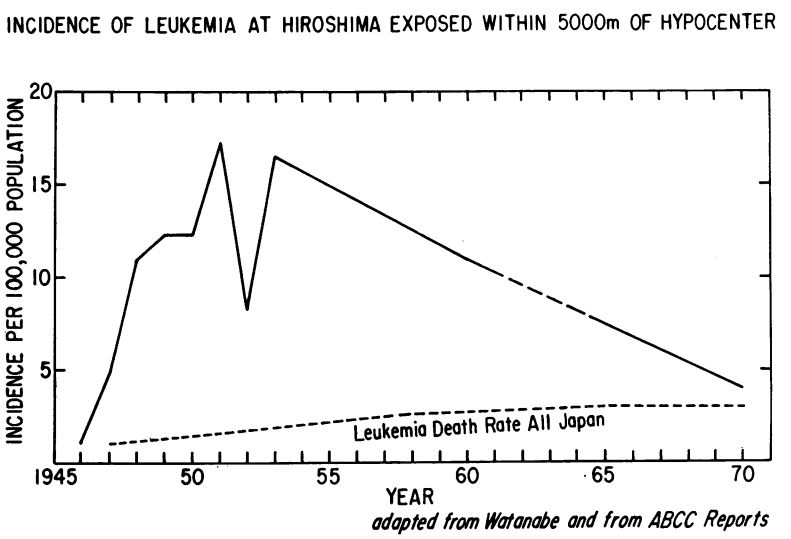

Fig. 7. Incidence of leukemia at Hiroshima among persons exposed within 5,000 meters of the hypocenter. Note the sharp rise in incidence subsequent to the atomic bombing and the decrease in incidence following the mid-1950s. Note also the steady increase in the death rate from leukemia for all Japan and the tendency of the rates in the two populations to approximate each other.

pathology of the bone marrow in those who died within a few months of exposure, noted foci of a typical cellular regeneration in a few and suggested that leukemia might well appear among the survivors. Unfortunately this prediction has been borne out. More than 400 cases have been reported, most of which were of acute myelogenous leukemia.[30] The bulk of the cases thus far reported[31] occurred between 1949 and 1960; the rate, now falling, is now nearing that for all Japan[30] (Figure 7). When the incidence of leukemia is related to distance from the hypocenter of the bomb explosion and thus to estimated dose there is an apparent correlation of increased incidence with dose at levels of 400 rads and above[8] (Figure 8).

These data from Japan, derived from persons who had received a single whole-body exposure, reinforce those reported by the late Dr. Court-Brown[32] as to the dose-effect relation in the development of leukemia among patients whose spinal column had been treated with x rays to relieve the pain of ankylosing spondylitis. In these partial-body, repeated exposures a linear relation could be deduced from the data,

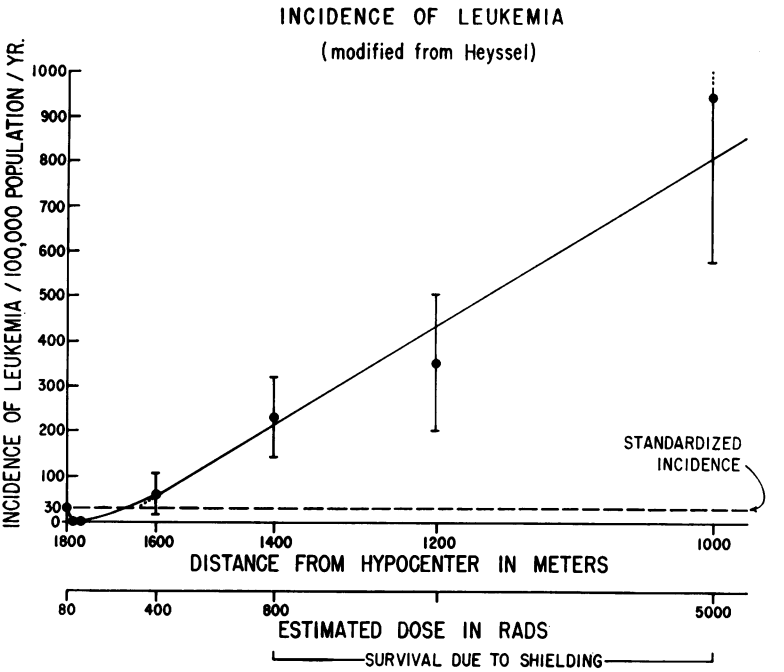

Fig. 8. Incidence of leukemia related to distance from the hypocenter in meters and the estimated dose in rads. Note the approximate linearity of response with increasing dose from 400 rads upward. Survivors in the upper range almost certainly had had partial shielding of their bodies. Reproduced by permission from: Warren, S. *The Pathology of Ionizing Radiation.* Springfield, Ill., Thomas, 1961.

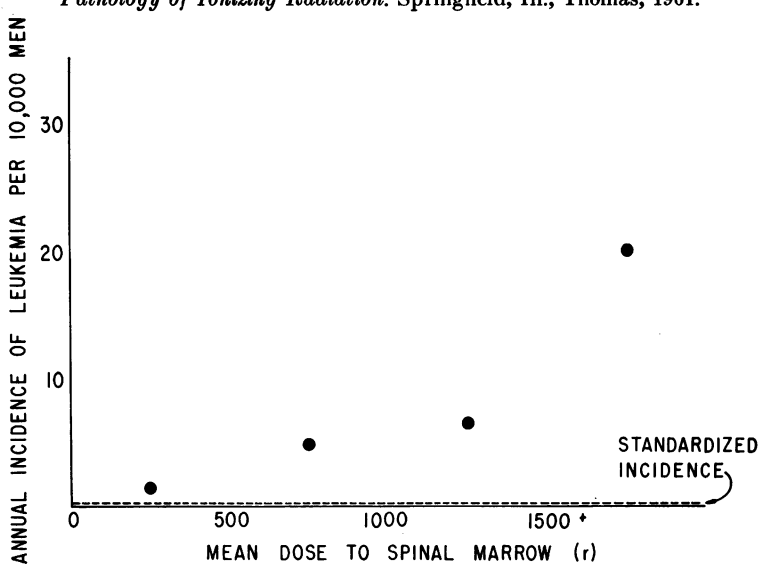

Fig. 9. Annual incidence of leukemia among cases of ankylosing spondylitis[32] with reference to mean dose to the spinal marrow. The data points only are plotted.

PATIENTS WITH CANCER OF THE CERVIX
AGE-ADJUSTED OBSERVED INCIDENCE PER 100,000 PER YEAR*

	Leukemia	*Lymphatic malignancy*	*All hematologic malignancy*
Radium alone	0	0	0
External therapy alone	0	0	0
Radium plus external therapy	8.4	12.7	21.0
No radiation	22.5	0	22.2
All patients	7.3	8.8	16.2
Expected rate	9.0	11.0	20.0

Leukemia and lymphatic malignancy observed in survivors of cervical cancer treated with and without radiation.
*Adapted from Hutchison, G.B.[33]

although the findings were reasonably compatible with a sigmoid type of curve as well (Figure 9).

A puzzling contradiction is found in the international study reported by Hutchison.[33] Here many clinics cooperated to report subsequent development of leukemia in those women treated for cancer of the cervix, many of whom had received radiation to a large portion of their hematopoietic tissue in the course of treatment (see accompanying table). No cases of hematologic malignancy appeared in those cases treated with radium alone and none with external radiation therapy alone. In those receiving a combination of the two the rate was 21/100,000; in those cases that received no radiation and were treated with surgery only the rate was 22/100,000; the expected rate was 20/100,000. In other words, in these patients with thousands of years at risk there was no increase in leukemia. This might be due to the fact that insufficient time has passed; this possibility will be indicated by the continuing character of this study. It might also mean that the considerable unirradiated portion of the marrow had protected the irradiated portion to some degree.

However it is clearly established that leukemia, usually but not always of the myeloid type, is induced in man by exposure to ionizing radiation, although the incidence-dose relation is less clearly established. The percentage of leukemia cases among those exposed is always small, usually under 5%. Apparently an exposure of less than 100 rads is not effective.

To summarize: adequate data have been obtained to establish a variety of types of ionizing radiation as a cause of cancer. This holds for a number of different kinds of malignant tumors derived from different cell types. The dose-effect relations are not clear, but in general a greater dose may be correlated with a higher-incidence rate of cancer. The mechanisms for radiation carcinogenesis are more probably multiple than single.

REFERENCES

1. Gross, L. "Spontaneous" leukemia developing in C3H mice following inoculation in infancy with AK leukemia extracts, or AK embryos. *Proc. Soc. Exp. Biol. Med. 76*:27, 1951.
2. Frieben, A. Cancroid . . . nach langdauernder Einwirkung von Röntgenstrahlen. *Fortschr. Röntgenstr. 6*:106, 1902.
3. Martland, H. S. The occurrence of malignancy in radioactive persons. *Amer. J. Cancer 15*:2435, 1931.
4. Evans, R. D., Keane, A. T., Kolenkow, R. J., Neal, W. R. and Shanahan, M. M. Radiogenic tumors in the radium and mesothorium cases studied at M.I.T. In: Mays, C. W. *et al. Delayed Effects of Bone-Seeking Radionuclides.* Salt Lake City, Univ. of Utah Press, 1969.
5. Sikl, H. Uber den Lungenkrebs der Bergleute in Joachimstahl (Tschechoslowakei). *Z. Krebsforsch. 32*:609, 1930.
6. U.S. Congress Joint Committee on Atomic Energy, Subcommittee on Research, Development, and Radiation. *Radiation Exposure of Uranium Miners.* Washington, D.C., Govt. Print. Off., 1968.
7. Toyooka, E. T., Pifer, J. W., Crump, S. L., Dutton, A. M. and Hempelmann, L. H. Neoplasms in children treated with x-rays for thymic enlargement. II. Tumor incidence as a function of radiation factors. *J. Nat. Cancer Inst. 31*:1357, 1963.
8. Brill, A. B., Tomonaga, M. and Heyssel, R. M. Leukemia in man following exposure to ionizing radiation: Summary of findings in Hiroshima and Nagasaki, and comparison with other human experience. *Ann. Intern. Med. 56*:590, 1962.
9. Wolbach, S. B. The pathological histology of chronic x-ray dermatitis and early x-ray carcinoma. *J. Med. Res. 21*:415, 1909.
10. Cade, Sir Stanford. Radiation-induced cancer in man. *Brit. J. Radiol. 30*:393, 1957.
11. Albert, R. E., Omran, A. R., Bauer, E. W., Dove, D. C., Cohen, N. C., Schmidt H., Baumring, R., Morrill, S., Schulz, R. and Baer, R. L. Follow-up study of patients treated by x-ray for tinea capitis. *Amer. J. Pub. Health 56*:2114, 1966.
12. MacMahon, H. E., Murphy, A. S. and Bates, M. I. Endothelial-cell sarcoma of liver following thorotrast injections. *Amer. J. Path. 28*:585, 1947.
13. Morken, D. A. and Scott, J. K. *The Effects on Mice of Continual Exposure to Radon and its Decay Products on Dust.* Univ. of Rochester, Atomic Energy Commission Project Report No. UR-669, 1966.
14. Meyer, E. C. and Liebow, A. A. Relationship of interstitial pneumonia honeycombing and atypical epithelial proliferation to cancer of the lung. *Cancer 18*:322, 1965.
15. Saccomanno, G., Archer, V. E., Saunders, R. P., James, L. A. and Beckler, P. A. Lung cancer of uranium miners on the Colorado plateau. *Health Phys. 10*:1195, 1964.
16. Socolow, E. L. and Hashizume, A. Thy-

roid carcinoma in man after exposure to ionizing radiation. *New Eng. J. Med. 268*:406, 1963.

17. Conard, R. A., Rall, J. E. and Sutow, W. W. Thyroid nodules as a late sequela of radioactive fallout: In a Marshall Island population exposed in 1954. *New Eng. J. Med. 274*:1391, 1966.
18. Bustad, L. K., George, L. A., Jr., Marks, S., Warner, D. E., Barnes, C. M., Herde, K. E. and Kornberg, H. A. Biological effects of I^{131} continuously administered to sheep. *Radiat. Res. 6:* 380, 1957.
19. Hempelmann, L. H. Risk of thyroid neoplasms after irradiation in childhood. *Science 160*:159, 1968.
20. Pifer, J. W., Hempelmann, L. H., Dodge, H. and Hodges, F. J. Neoplasms in Ann Arbor series of thymus-irradiated children: A second survey. *Amer. J. Roentgen. 103*:13, 1968.
21. March, H. C. Leukemia in radiologists. *Radiology 43*:275, 1944.
22. Ulrich, H. Incidence of leukemia in radiologists. *New Eng. J. Med. 234*:45, 1946.
23. Henshaw, P. S. and Hawkins, J. W. Incidence of leukemia in physicians. *J.A.M.A. 4*:339, 1944.
24. Warren, S. Longevity and causes of death from irradiation in physicians. *J.A.M.A. 162*:464, 1956.
25. March, H. C. Leukemia in radiologists, ten years later: With review of pertinent evidence for radiation leukemia. *Amer. J. Med. Sc. 242*:137, 1961.
26. Warren, S. and Lombard, O. M. New data on the exposure of the human population to ionizing radiation. Proc. 11th Internat. Congress of Radiology, Excerpta Medica Internat. Congress Series No. 105, pp. 1508-13, 1967.
27. Warren, S. and Lombard, O. M. Mortality and radiation exposures of Massachusetts dentists. *J. Amer. Dent. Assoc.* In press.
28. Liebow, A. A., Warren, S. and DeCoursey, E. Pathology of atomic bomb casualties. *Amer. J. Path. 25*:853, 1949.
29. Oughterson, A. W. and Warren, S. *Medical Effects of the Atomic Bomb in Japan.* Division VIII—Vol. 8. National Nuclear Energy Series. Manhattan Project Technical Section. New York, McGraw-Hill, 1956.
30. Atomic Bomb Casualty Commission, Fact Book, 1969 ed. Tabular and graphic presentation of ABCC research findings.
31. Bizzozero, O. J., Jr., Johnson, K. G. and Giocco, A. Radiation-related leukemia in Hiroshima and Nagasaki, 1946-1964. I. Distribution, incidence and appearance time. *New Eng. J. Med. 274*:1095, 1966.
32. Court-Brown, W. M. and Doll, R. *Leukaemia and aplastic anaemia in patients irradiated for ankylosing spondylitis.* Medical Research Council Report 295. London, Her Majesty's Stationery Office, 1957.
33. Hutchison, G. B. Leukemia in patients with cancer of the cervix uteri treated with radiation. A report covering the first 5 years of an international study. *J. Nat. Cancer Inst. 40*:951, 1968.